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In the Supreme Court of the United States

OCTOBER TERM, 1995

SCHERING CORPORATION, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR THE RESPONDENT IN OPPOSITION

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QUESTION PRESENTED

Under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.* (FDCA), a drug manufacturer can receive approval from respondent Food and Drug Administration (FDA) for a new generic drug through an abbreviated application procedure (21 U.S.C. 355(j)), if the manufacturer establishes that the generic drug is bioequivalent to a drug previously approved by the FDA. The question presented is:

Whether the FDA's regulation, 21 C.F.R. 320.1(e), implementing one of the statutory bioequivalence provisions constitutes a reasonable interpretation of the FDCA.

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OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-21a) is reported at 51 F.3d 390. The opinion of the district court (Pet. App. 22a-31a) is reported at 866 F. Supp. 821.

JURISDICTION

The judgment of the court of appeals was entered on April 3, 1995. The petition for a writ of certiorari was filed on July 3, 1995. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATEMENT

1. The Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.* (FDCA), provides that manufacturers of new generic drugs can obtain approval for their products from respondent, the Food and Drug Administration (FDA), through an abbreviated application procedure, without the clinical testing that is necessary as part of a new drug application procedure. To obtain FDA approval for a generic drug under the abbreviated procedures, the manufacturer must establish, inter alia, that its generic drug is bioequivalent to a drug that previously was approved by the FDA. See 21 U.S.C. 355(b); 21 U.S.C. 355(j)(2)(A)(iv). Bioequivalence occurs "when two drugs possess the same efficacy." Pet. App. 5a.

The FDCA describes two circumstances in which a drug "shall be considered to be bioequivalent" to another drug. Section 355(j)(7)(B), which was added in 1984 as part of the expansion of the abbreviated application procedure, provides:

> A drug shall be considered to be bioequivalent to a listed drug if—
>
> (i) the rate and extent of absorption[1] of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental

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[1] Absorption describes the process by which an active drug ingredient enters the body's physical system. Systemic absorption is the process by which a drug is introduced into the bloodstream, as occurs when a pill is taken orally or a drug is injected directly into the bloodstream.

conditions in either a single dose or multiple doses; or

(ii) the extent of the absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

21 U.S.C. 355(j)(7)(B).

In 1992, the FDA promulgated regulations implementing the bioequivalence requirements for generic drugs approved under the 1984 abbreviated application procedure. The regulation implementing subpart (i) of Section 335(j)(7)(B) defines bioequivalence as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose and under similar conditions in an appropriately designed study." 21 C.F.R. 320.1(e).

2. Petitioner, a manufacturer of certain pioneer [2] drug products previously approved by the FDA, filed

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[2] A pioneer drug is the first drug product, defined by its particular active ingredient, to receive FDA approval for a specified use. Pet. App. 2a

suit in the United States District Court for the District of New Jersey claiming that the FDA's reguation defining bioequivalence, 21 C.F.R. 320.1(e), is invalid. Petitioner argued that the statutory provisions regarding bioequivalence, 21 U.S.C. 355(j)-(7)(B)(i) and (ii), constitute the only permissible definitions of bioequivalence and that these definitions call for an assessment of the actual absorption of drug products by the body. Petitioner contended that the FDA's regulation impermissibly broadens that statutory definition by replacing the statutorily prescribed measurement of drug absorption with a measurement that assesses when the drug becomes available at the site of action.[3]

The district court denied petitioner's motion for summary judgment and entered summary judgment for the FDA. Pet. App. 22a-32a.[4] The court adopted the reasoning of an earlier issued opinion of the United States District Court for the District of Columbia. *Schering Corp.* v. *Sullivan*, 782 F. Supp. 645 (1992), vacated as moot, 995 F.2d 1103 (D.C. Cir.

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[3] Petitioner argued that the bioequivalent standard based on absorption set forth in the FDCA could not be met for certain of its pioneer products that are non-systemically effective drugs, i.e. medications effective through topical application, such as ointments and mist inhalers. Therefore, under petitioner's interpretation and absent the FDA regulation defining bioequivalence to focus on availability, generic drugs claiming to be copies of petitioner's non-systemically effective drugs could not be approved through the abbreviated procedure because the abbreviated procedure requires the absorption bioequivalent determination. See Pet. App. 4a-5a.

[4] The district court rejected the FDA's challenge to petitioner's standing to maintain the action, as did the court of appeals. Pet. App. 26a-30a; *id.* at 13a.

1993) (set forth at Pet. App. 33a-49a). That opinion arose out of an action petitioner had commenced in 1989, seeking a declaration from the FDA that, inter alia, the bioequivalence requirement in the 1984 abbreviated application procedure could be met only by satisfying one of the two circumstances set forth in 21 U.S.C. 355(j)(7)(B). The district court in the earlier case had rejected petitioner's claim and entered summary judgment for the FDA.[5] Consistent with that ruling, the district court below granted summary judgment to the FDA, concluding that "Congress had not set forth an exclusive definition of 'bioequivalent.'" Pet. App. 31a.

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[5] Petitioner had petitioned the FDA in 1989 to deny all abbreviated applications for approval of non-systemically effective drugs. The FDA denied the petition and petitioner sought judicial review. The district court granted the FDA summary judgment. Pet. App. 33a-49a. The district court rejected petitioner's claim that 21 U.S.C. 355(j)(7)(B) provided the exclusive means for determining the bioequivalence required in the abbreviated application procedure. Pet. App. 43a. The court applied the two-step analysis in *Chevron U.S.A. Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), and concluded that the congressional intent behind Section 355(j)(7)(B) is clear and that "Congress permitted the FDA to retain its historically wide discretion in defining showings of 'bioequivalence.'" Pet. App. 32a. The court also held, alternatively, that even if the FDCA is ambiguous or silent on the issue, the FDA's interpretation is valid because it is a reasonable interpretation in light of the absence of any evidence that Congress intended to override the FDA's practice of accepting alternative showings of bioequivalence. *Id.* at 38a, 43a-44a. The case ultimately was dismissed as moot on appeal, and the district court opinion vacated, in light of the intervening promulgation of the regulation, defining bioequivalence, which is at issue in this case. *Schering Corp.* v. *Shalala*, 995 F.2d 1103 (D.C. Cir. 1993).

3. The court of appeals affirmed. Pet. App. 1a-21a. Applying the two-step analysis in *Chevron U.S.A. Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), the court held that the language of Section 355(j)(7)(B) is ambiguous, and that the FDA's regulation, 21 C.F.R. 320.1(e), is a permissible construction of the statute. Pet. App. 3a, 16a-19a.

With regard to the first step of the *Chevron* analysis—whether the statute is ambiguous—the court of appeals disagreed with the district court's conclusion that Section 355(j)(7)(B) unambiguously does not constitute an exclusive definition of "bioequivalent." The court of appeals also disagreed, however, with petitioner's argument that Section 355(j)(7)(B) is unambiguously exclusive. Instead, the court of appeals concluded that Section 355(j)(7)(B) is ambiguous.

The court acknowledged that Section 355(j)(7)(B) is couched in terms different from the immediately preceding Section, which unambiguously constitutes an exclusive definition of another term. See 21 U.S.C. 335(j)(7)(A).[6] Nonetheless, the court of appeals declined to find that the difference in language meant that Section 335(j)(7)(B) was unambiguously intended not to be an exclusive definition. The court found instead that the difference in language renders Section 355(j)(7)(B) ambiguous and that that determination is reinforced by other provisions of the FDCA that indicate that Congress envisioned the use

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[6] That Section provides:

> (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

21 U.S.C. 335(j)(7)(A).

of more than the one method of determining bioequivalence. Pet. App. 15a-17a. The court found that the legislative history of the 1984 Amendments that added Section 355(j)(7)(B) to the FDCA does not alter that conclusion.

Turning to the second step of the *Chevron* analysis—whether the agency's interpretation of the ambiguous statute is reasonable—the court of appeals agreed with the district court that the FDA's interpretation is a permissible construction of the FDCA. The court of appeals reasoned that the 1984 Amendments to the FDCA were intended to be a means for extending the abbreviated approval process, and there was no evidence that Congress intended to restrict the FDA's discretion in determining the bioequivalence of drugs for purposes of that process. Pet. App. 18a, citing H.R. Rep. No. 857, 98th Cong., 2d Sess. Pt. I (1984). The court emphasized the fact that, in enacting Section 355(j)(7)(B) in 1984, Congress relied on the FDA's 1977 regulations which indicated that different means could be used to determine bioequivalence.[7] The court recognized that Congress intended through the 1984 Amendments to extend that approach to generic drugs copying drugs first approved after 1962. Pet App. 19a.[8] The court found that

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[7] The FDA's 1977 bioequivalence regulations, 21 C.F.R. 320.1-320.62, applied both to drugs intended for systemic absorption and to non-systemically effective drugs, and provided for bioequivalence to be established by means other than actual measurement of rate and extent of absorption for non-systemically effective drugs. See 21 C.F.R. 320.22, 320.24, 320.53, 320.57 (1977).

[8] Before the addition of Section 355(j)(7)(B) as part of the broadening of the abbreviated application procedure in 1984, the

the FDA's preferred method "was to determine bioequivalence on a case-by-case basis depending on the drug under consideration for approval pursuant to an * * * abbreviated application." *Ibid.* It concluded that "[t]he FDA is the agency charged with implementing the Food, Drug and Cosmetic Act as amended. Its judgments as to what is required to ascertain the safety and efficacy of drugs fall

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procedures for FDA approval of a generic drug depended on whether the drug being copied had been previously approved by the FDA before 1962. Before 1962, the FDA had approved a new drug if it was safe for its intended use. The Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, however, required manufacturers of new drug products to demonstrate that their products were not only safe but also effective for their intended uses in order to obtain FDA approval. After the 1962 Amendments, the FDA conducted its own examination, through the Drug Efficacy Study Implementation program (DESI), to determine whether the drugs it had approved as safe before 1962 were effective. See *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 613-615 (1973). In light of these determinations of efficacy, the FDA decided to accept abbreviated new drug applications for generic copies of drugs it had found to be effective under the DESI program. The FDA required the abbreviated applications to contain information demonstrating that the product was bioequivalent to the previously approved drug. Full new drug applications were still required for generic versions of drugs first approved after 1962, however, because they had not been subject to DESI review. See *Tri-Bio Laboratories, Inc.* v. *United States*, 836 F.2d 135, 138 (3d Cir. 1987), cert. denied, 488 U.S. 818 (1988). Thus, the 1984 Amendments were intended to extend the abbreviated approval process for generic drugs to generic drugs that copied drugs approved after 1962.

squarely within the ambit of the FDA's expertise and merit deference from us." *Id.* at 19a.[9]

ARGUMENT

Petitioner contends (Pet. 16-23) that the court of appeals' opinion is contrary to the language, structure and history of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, and that 21 U.S.C. 355(j)(7)(B) unambiguously establishes an exclusive definition of bioequivalence. Pet. 17-18. Petitioner contends (Pet. 23-27) that the court of appeals erred in upholding the FDA's regulation, 21 C.F.R. 320.1(e), as a permissible interpretation of the FDCA because the court "fundamentally misunderstood" the congressional purpose behind the addition of Section 355(j)(7)(B) to the FDCA in 1984. Pet. 25.

The court of appeals correctly rejected petitioner's arguments, as did the two district courts that have addressed them. The court of appeals' opinion reflects a straightforward—and correct—application of this Court's precedents on statutory construction. Petitioner acknowledges that there is no relevant circuit conflict. Pet. 15-16.

Section 355(j)(7)(B) cannot reasonably be read as an unambiguous statement of an exclusive definition.

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[9] Petitioner also had sought injunctive relief to prohibit the FDA from releasing certain safety and efficacy data regarding its products. See Pet. App. 7a n.4. That request for relief was dependent on a favorable finding on the merits and was therefore denied by the district court and the court of appeals. *Id.* at 7a n.4, 20a. The court of appeals also rejected petitioner's challenge to the district court's treatment of the FDA's motion for judgment on the pleadings as a motion for summary judgment. *Id.* at 20a-21a. Petitioner does not raise these issues in this Court.

See Pet. App. 13a-17a. Section 355(j)(7)(B) sets forth two circumstances in which a drug "shall be considered" to be bioequivalent to another drug. The Section's plain language does not state that the meaning of "bioequivalent" is limited to those two circumstances. In contrast, the immediately preceding Section of the statute contains limiting language and is couched in terms of what that term "means." See 21 U.S.C. 355(j)(7)(A). Moreover, as the court of appeals recognized, other Sections of the FDCA implicitly acknowledge that other means of determining bioequivalence are permitted. Those Sections reinforce the conclusion that Section 355(j)(7)(B) is not an unambiguous, exclusive definition of bioequivalence. See Pet. App. 16a-17a, citing 21 U.S.C. 355(j)(6)(A)(i)(III).

Thus, the language and structure of the FDCA are consistent with the FDA's interpretation that Section 355(j)(7)(B) functions as a safe harbor. The Section establishes two circumstances in which the FDA is required to find that a drug is a bioequivalent, but the statute permits the FDA to determine bioequivalence using additional methods.

The history of the 1984 Amendments to the FDCA also supports the FDA's interpretation. By adding the broader abbreviated application procedure in 1984, Congress intended to make available a greater number of safe and effective low-cost generic drugs. Congress sought to achieve this goal by extending the abbreviated application procedure and requiring a finding of bioequivalence as a part of the procedure, but it did not dictate the exclusive means by which the bioequivalence finding must be made. Pet. App. 18a. Most significantly, "[a]lthough the [1984 Amend-

ments] mandated a showing of bioequivalence for approval, there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of [the abbreviated] approval. To the contrary, the expressed desire of Congress was to extend the then-current FDA abbreviated application practices to drugs first approved post-1962." Pet. App. 18a-19a.

The FDA's method for determining bioequivalence relies on a case-by-case approach that depends on the charactristics of the drug under consideration. Absent an expressed contrary congressional intent, that judgment of the agency charged with implementing the FDCA merits deference. Pet. App. 19a. The court of appeals properly recognized the "considerable weight [that] should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer, and [that] the principle of deference to administrative interpretations 'has been consistently followed by this Court whenever decision as to the meaning or reach of a statute has involved reconciling conflicting policies'." *Chevron*, 467 U.S. at 844 (footnote omitted). The FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference." Pet. App. 19a.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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